

Radical Reoperation for Advanced Pancreatic Carcinoma

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The indications and outcomes of aggressive reoperation in patients referred to the National Cancer Institute (NCI) for protocol therapy of locally advanced pancreatic carcinoma were investigated. Twenty-nine patients referred to the NCI after exploration and determination of unresectability elsewhere were considered to have localized disease after a metastatic work-up. These patients were then entered onto NCI adjuvant therapy protocols and taken to exploratory laparotomy. Intraoperatively, patients underwent complete resection if possible; otherwise varying palliative surgical procedures were performed. Of the 29 patients, 16 underwent complete resection of their disease, and 13 were unresectable. Two patients suffered postoperative mortality. Disease-specific survival of the resected patients was significantly better than that of the unresectable patients ($P < 0.01$). The two long-term survivors (53 and >109 months) underwent definitive surgery after a palliative procedure elsewhere. Complete resection of pancreatic carcinoma contributes to increased survival. The intraoperative definition of unresectability in pancreatic cancer varies with the degree of pancreatitis present, the surgical expertise of the surgeon, and the available ancillary services. Given the extremely grave prognosis of patients with unresectable pancreatic carcinoma, locally unresectable patients without peritoneal seeding or distant metastases at exploration should be considered for referral for protocol therapy to centers where expertise in radical surgery for pancreatic cancer exists. © 1996 Wiley-Liss, Inc.*

KEY WORDS: adjuvant therapy, pancreatic cancer, resection

INTRODUCTION

The Surgery and Radiation Oncology Branches of the National Cancer Institute (NCI) performed trials of adjuvant therapy in pancreatic carcinoma in the early 1980s. Since the NCI relies exclusively on referrals for its patient base, most of these patients had previously undergone a significant work-up, often including laparotomy, prior to referral. This paper describes the NCI experience with aggressive re-exploration of patients with locally advanced pancreatic carcinoma, who were deemed unresectable elsewhere.

PATIENTS AND METHODS

Between 1980 and 1984, patients were referred to the NCI for consideration of protocol therapy for pancreatic

carcinoma. All patients underwent metastatic screening which included history and physical examination, blood work to include liver-associated enzymes, chest radiography, and abdominal imaging. Full review was made of prior operative notes in patients who had undergone surgical procedures. Forty-nine patients were considered to have localized disease after this work-up; they were taken to exploratory laparotomy. If patients were able to have

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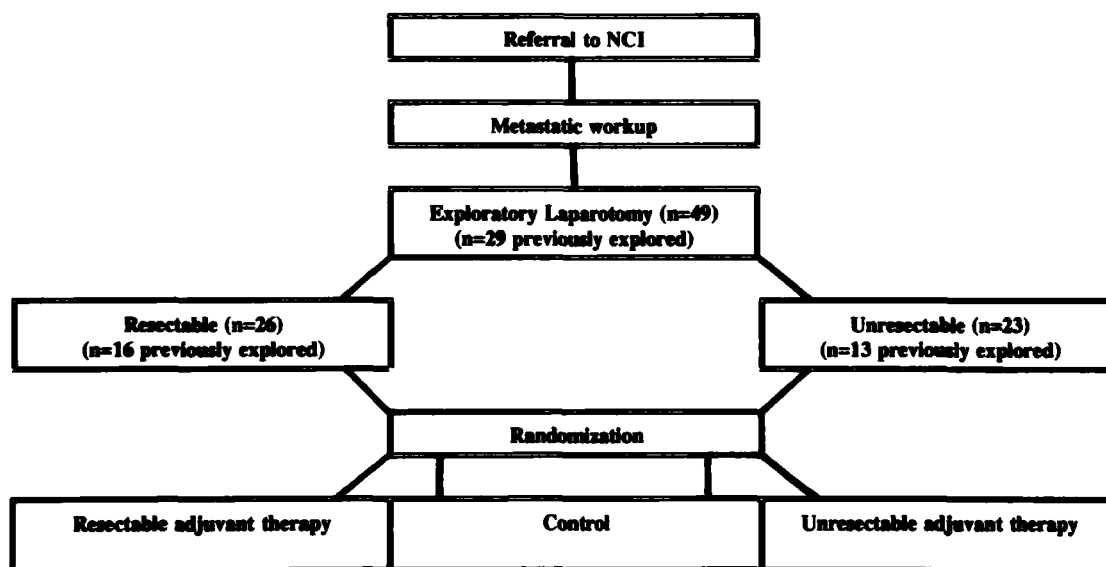


Fig. 1. Schema of the NCI pancreatic carcinoma trials. Of the 49 patients taken to laparotomy, 29 had previously been explored. These patients are the subject of this report.

all gross disease removed at time of laparotomy, they underwent definitive surgery. These patients were randomized to receive or not receive adjuvant intraoperative radiotherapy (IORT). If patients had disease noted intraoperatively which was considered unresectable, they underwent varying degrees of palliative surgery and were randomized to an adjuvant radiotherapy protocol of conventional external beam radiotherapy (EBRT) with or without IORT. Misonidazole was delivered to those patients receiving IORT, and 5-fluorouracil chemotherapy was administered postoperatively to patients who were unresectable. Resectable patients who did not receive IORT received postoperative EBRT in most instances.

Figure 1 depicts the study schema. Patient accession was halted in 1984. Complete results of the randomized trials will be addressed separately. All protocols were approved by the NCI institutional review board regarding protection of human subjects.

This paper analyzes a subset of patients accrued to the NCI trials: 29 patients referred after prior surgical exploration elsewhere, where the patients had been declared to be unresectable by the referring physicians. On NCI review, the following criteria were used to determine eligibility for re-exploration: a) computer-aided tomographic (CT) studies of the chest, abdomen, and pelvis without evidence of visceral metastases; b) bone scintigraphy negative for metastases; and c) arteriography revealing no obvious encasement of the superior mesenteric artery, celiac axis, or proper hepatic artery, with the venous phase showing patency of the portal system. Partial portal vein involvement or malignant stenosis was allowed, but complete obstruction of the portal or superior mesenteric veins was a contraindication to re-exploration.

At time of laparotomy at the NCI, 13 patients were

confirmed as unresectable and 16 patients subsequently underwent surgical resection of all gross disease. Intraoperative determination of resectability was based on: a) the absence of visceral metastases or peritoneal seeding; b) the lack of direct tumor invasion into the vena cava, liver, proximal stomach, or kidney; c) the absence of evidence of complete portal vein or superior mesenteric vein occlusion, or the absence of neoplastic involvement of two or more upper abdominal visceral arteries (hepatic, celiac, or superior mesenteric). Segmental tumor involvement of the portal venous system or of one major artery allowed resection with appropriate vascular reconstruction.

Of patients considered resectable, those with primary lesions confined to the pancreatic head and those <2.5 cm in size underwent pancreaticoduodenectomy. Patients underwent total pancreatectomy for large (>2.5 cm) lesions, for lymph node involvement, or in the presence of a soft distal gland with which it was considered to be unsafe to perform an anastomosis. Regional pancreatectomy was delivered to patients when vascular involvement was present. Given the nature of the anatomy, resection margins were generally close. In one case, a microscopically positive margin was reported in a completely resected patient: on the root of the superior mesenteric artery.

Survival rates were generated using the method of Kaplan and Meier [1]. Comparisons between survival curves were performed using a Mantel-Haenszel technique [2]. Median follow-up was 109 months.

RESULTS

The characteristics of the 29 patients who were re-explored after prior surgical exploration are listed in Table

TABLE I. Characteristics of Patients Taken to Re-Exploration on Two Pancreatic Cancer Protocols at the NCI

Characteristic	Resectable cohort (n = 16)	Unresectable cohort (n = 13)
Age		
Median	55	57
Range	25–65	28–66
Prior surgery ^a		
Biopsy alone	1	4
Diagnostic laparoscopy	—	2
Choledochoduodenostomy	6	—
Cholecystoduodenostomy	1	—
Cholecystojejunostomy	7	4
Gastrojejunostomy	—	3
Not stated	1	3
Interval between surgeries		
Median	1.5 months	2 months
Range	3 weeks–4.5 months	1 week–7 months
Salvage surgery ^a		
Pancreaticoduodenectomy	1	—
Total pancreatectomy	9	—
Regional pancreatectomy	6	—
Biopsy	—	4
Cholecystojejunostomy	—	6
Choledchojejunostomy	—	2
Gastrojejunostomy	—	7
Jejunojejunostomy	—	4
Nodal status		
Positive	8	— ^b
Negative	8	— ^b

^aSome patients had more than one procedure performed.^bNodal determination was not routinely performed in unresectable cases.

I. All patients had histologically documented adenocarcinoma of the pancreatic head. Adjuvant therapy has not been shown on preliminary analysis to affect survival in this trial.

Sixteen patients underwent definitive surgery at re-exploration. Two patients died within 30 days of surgery. One patient who was otherwise recovering uneventfully suffered a myocardial infarction 2 weeks postoperatively. The other patient developed mesenteric arterial thrombosis with bowel infarction and septicemia, dying on the 29th postoperative day of multisystem failure. There was no indication preoperatively that these two patients were at any greater risk for complications at re-exploration. The remaining 14 patients survived a median of 14.5 months postoperatively. One patient was alive and without evidence of disease 109 months postoperatively, and one patient died of other causes without evidence of disease 53 months postoperatively.

Thirteen patients were unresectable for a variety of reasons (Table II), although liver metastases were noted in most cases. In no cases had these been apparent at any point in the clinical evaluation; nor were they noted at the time of surgery prior to NCI referral.

Overall survival of the resected patients was not significantly different than that of the unresectable patients. However, disease-specific survival was significantly better for resected patients than for unresected ($P < 0.01$).

TABLE II. Reasons for Unresectability of Patients Re-Explored for Pancreatic Cancer at the NCI

Reason	Number of patients
Hepatic metastases	8
Venous varices	2
Peritoneal implants	3

Disease-specific survival curves for the completely resected and unresectable cohorts are shown in Figure 2.

DISCUSSION

It is clear that the only patients with pancreatic cancer who are candidates for cure are those with completely resected disease. These select patients are infrequently encountered, comprising only 8% of the Gastrointestinal Tumor Study Group pancreatic cancer trials [3]. Even among these patients able to be resected, success is not ensured in most cases. In a recent analysis of autopsy- and laparotomy-documented patterns of failure in the completely resected cohort of the NCI pancreatic cancer trials [4], almost half of patients failed locally or regionally, over a third failed with peritoneal seeding, and almost two thirds failed with distant metastases.

In pancreatic carcinoma, several authors have described a potential role for staged reoperation despite prior

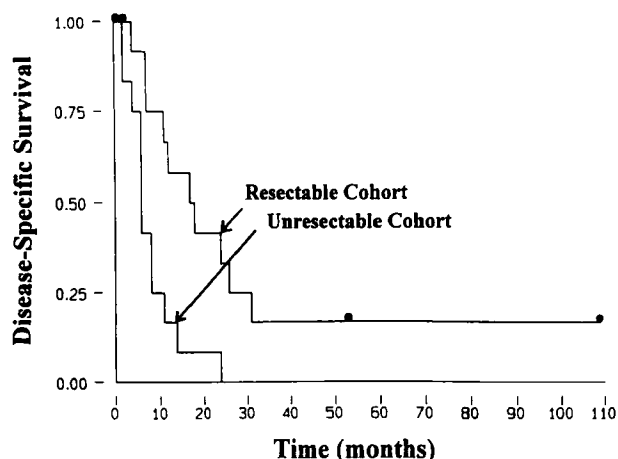


Fig. 2. Kaplan-Meier plot of disease-specific survival for the resectable and unresectable cohorts of patients with pancreatic cancer who were taken to re-exploration. Darkened circles represent censored data.

intraoperative determination of unresectability (Table III). In Fortner's experience [5], 77% of patients who underwent successful regional pancreatectomy have been previously declared unresectable at laparotomy. Similarly, Jones et al. [6] reported that 50 of their 98 patients with perampullary lesions had undergone prior surgeries. Detailed discussion of the results of reoperation in their patients is not specifically provided.

Moossa [7] described re-exploration in 17 of 24 patients referred to the University of Chicago with locally advanced disease who previously had been considered unresectable and surgically palliated. Nine patients were resectable; two additional patients had no evidence of carcinoma on multiple biopsies and were long-term survivors.

Further data are available in a series reported by Hashimi and Sabanathan [8]. One hundred-twelve patients with pancreatic or perampullary carcinoma were considered locally unresectable at laparotomy, and underwent palliative bypass procedures. Thirty patients so treated recovered promptly and gained weight, so that re-exploration was considered 3 months postoperatively.

Another metastatic work-up was performed which revealed 18 patients with persistent local disease only. Eleven patients underwent complete excision of disease at reoperation, with two 5-year survivors. The reason for unresectability at the first exploration was considered to be pancreatitis and not tumor burden. Similar results have been reported from Johns Hopkins [9] and the M. D. Anderson Cancer Center [10]. In the first study, 33 of 46 patients taken to repeat exploratory laparotomy were found to be resectable. All patients with nonpancreatic perampullary carcinoma were resected. At M. D. Anderson, 23 patients were considered to be potentially resectable after a second work-up; 14 had complete resections at laparotomy.

Of the 29 patients referred for unresectable disease in the NCI experience, 14 tolerated complete resection and survived the perioperative period. The salvage rate is thus 14 of 29 patients (48%). These patients are clearly highly selected by virtue of an intersurgery interval without disease progression and a repeat work-up without evidence of metastases. Nevertheless, they were afforded an opportunity for longer survival by the second, more radical, surgery. The effect of that surgery is shown by the increased disease-specific survival in this cohort. The two long-term survivors of these protocols had undergone palliative bypass prior to referral to the NCI, and were considered unresectable by conventional criteria.

Honest appraisal of the NCI data indicates that the absence of an overall survival difference between the resectable and unresectable cohorts is due in large part to postoperative mortality. Another criticism which may be raised from a statistical perspective is that a cohort of patients from two larger trials is analyzed. The point remains, however, that the potential for increased survival in completely resected patients in our experience and in that of other authors [5–10] is due principally to referral to a center which performs radical pancreatic resections routinely. Otherwise, for those patients, there would be inevitable and inexorable progression of disease left in situ.

The surgical effects of such robust surgical procedures

TABLE III. Re-Exploration of Patients With Unresectable Pancreatic Cancer: Experiences From the Literature

Author (reference)	Patients re-explored	Number resectable (%)
Fortner [5]	NS	28 (NS) ^a
Jones et al. [6]	50	NS
Moossa [7]	17	11 (65)
Hashimi and Sabanathan [8]	18	11 (61)
McGuire et al. [9]	46	33 (72)
Tyler and Evans [10]	23	14 (61)
Johnstone and Sindelar (this article)	29	16 (55)

^aNS = data not stated.

are also reflected in the mortality rates under these circumstances. While radical re-exploration may be a valuable option in experienced hands, its use must be tempered by the realization that it is inherently a much riskier procedure.

It is well described that complete resection is the single most important factor in survival of patients with adenocarcinoma of the pancreatic head. The fact remains that in the absence of frank distant metastases or peritoneal seeding, local unresectability is an intraoperative decision based on the surgeon's perspective and abilities, and the availability of ancillary medical support. In smaller practices, if locally advanced pancreatic carcinoma is discovered intraoperatively, referral to a nearby major medical center should be considered. A case may be made for expeditious referral; this theoretically would allow less time for potential disease progression before re-exploration.

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COMMENTARY

Surgical resection remains the only potentially curative treatment strategy for patients with adenocarcinoma of the pancreatic head. Patients who undergo successful resection of the primary tumor combined with either pre- or postoperative chemoradiation have a 5-year survival rate of up to 20% and a median survival of 18-19 months [1]. In contrast, patients with locally advanced, unresectable disease treated with palliative chemoradiation have a median survival of only 10-12 months, with virtually no chance for long-term survivorship [2]. Importantly, patients who undergo pancreaticoduodenectomy but are found to have a positive margin of resection also have a median survival of only 10 months [1,3]. Therefore, it is essential that surgery be applied only to patients with localized, potentially resectable pancreatic cancer. Traditionally, however, only one third of patients who undergo operations with curative intent have their pancreatic cancers successfully removed; the remaining patients are found to have unsuspected liver or peritoneal metastases or, most commonly, local tumor extension to the superior mesenteric vein or artery [4]. These patients undergo a large operation associated with an often prolonged recovery period yet survive less than 1 year [5]. Further, laparotomy for palliation in this subgroup of

patients is often unnecessary because of recent advances in endoscopic, percutaneous, and laparoscopic methods of biliary decompression. Therefore, in the absence of significant innovations in systemic therapy, the only potential for major improvements in the quality of life of patients with pancreatic cancer lies in our ability to limit surgery-related toxicity to those patients most likely to benefit from surgical intervention (i.e., to avoid laparotomy in patients with unresectable disease). Therein lies the importance of how the clinician defines resectability. The lack of a clear definition of resectability is largely responsible for patients seeking a second opinion regarding local tumor resectability following an initial unsuccessful attempt at tumor removal.

The article by Johnstone and Sindelar in this issue of the *Journal of Surgical Oncology* reports the NCI's experience with reoperative pancreatectomy. The magnitude of the operation involved in reoperative pancreatic surgery combined with the modest median survivals achieved emphasizes the need for a more precise definition of resectability based upon accurate preoperative imaging studies. Traditional means of intraoperative assessment of tumor resectability by palpation at the time of Kocher maneuver and establishment of a tumor-free plane between the superior mesenteric-